Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1392853

J Med Palliat Care. 2023;4(6):630-636

Predictive factors for acute pancreatic and peripancreatic fluid development in patients with acute pancreatitis

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Cite this article as: Coşkun MV, Karaahmetoğlu S, İnan O, Kurtipek AC. Predictive factors for acute pancreatic and peripancreatic fluid development in patients with acute pancreatitis. *J Med Palliat Care*. 2023;4(6):630-636.

Received: 18.11.2023 ◆ **Accepted**: 06.12.2023 ◆ **Published**: 31.12.2023

ABSTRACT

Aims: Acute fluid collections after acute pancreatitis carries risk of serious complications as infected pseudocyst and Wall off Necrose development. Hence, it is important to predict the development of acute fluid collections for treatment and management of acute pancreatitis. In this study, it is aimed to investigate predictive factors for development of acute fluid collections in patients with acute pancreatitis.

Methods: Total of 438 patients diagnosed with acute pancreatitis were screened. According to the Revised Atlanta Classification fluid development after acute pancreatitis was determined and the relationship between fluid development and the hematological/biochemical parameters of the patients at the time of admission was investigated. The best cut-off point of laboratory measurements for fluid development was determined by ROC analysis and the factors that may be most decisive in distinguishing between the patients with and without fluid development were determined by multivariate forward stepwise logistic regression analysis.

Results: It is found that developing acute fluid collections after acute pancreatitis was higher in patients with younger age and male gender. Also the risk of developing acute fluid collections after acute pancreatitis was found to be 6.2 times higher in patients with CRP/Albumin ratio greater than 1.09; 2.5 times higher in patients with ALP below 199.5 U/L; 1.9 times higher in patients with WBC greater than 11,6 $\times 10^9$/L and 1.5 times higher in patients with PLR above 197.1. Also the risk of developing acute necrotic collections after acute pancreatitis was 3 times higher in patients with serum calcium level below 8,6 mg/dl.

Conclusion: It has been determined that, presence of high CRP/albumin ratio, high NLR and low serum ALP level can be used as an indicator in predicting acute pancreatic and peripancreatic fluid development.

Keywords: Acute fluid collections, acute necrotic collection, acute pancreatitis, acute peripancreatic fluid collections

This article was presented orally at the 24th National Congress of Internal Medicine, 19-23 October 2022, Antalya, Turkey

INTRODUCTION

Acute pancreatitis (AP) is an important disease that can progress to multiple organ failure and have a high health cost all over the world. While the annual incidence of AP is reported as 33-74 per 100000 and its mortality is 1-8.9% in the world-wide studies, it is stated that it cost over 2.6 billion dollars per year.[1-3] Pancreatic and peripancreatic fluid collection development is seen in 30-60% of patients in AP, and it has been reported that hospital stay and morbidity are higher in patients with fluid development.[3,4] The data on predicting pancreatic and peripancreatic fluid development in AP is limited, and most of them based on out dated studies and defined by the old Atlanta Classification terminologies. Due to these studies, alcoholic etiology, low serum alkaline phosphatase level, presence of ascite, presence of pleural efusion, male gender, palpable mass on physical examination and presence of a high computed tomography severity index (CTSI) shown to be associated with pseudocyst formation.[5,6]

According to the recently updated Revised Atlanta Classification, fluid collections developing after AP were divided into 4 groups and defined in detail. Fluid collections present for less than 4 weeks are classified as acute peripancreatic fluid collection (APFC) and acute necrotic collection (ANC). Collections that persist for more than 4 weeks have been identified as pseudocysts and walled-off necrosis (WON).[7]

Fluid collections developping in acute period have an important place in the prognosis of AP in terms of their ability to evolve into chronic fluid collections and become

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infected.[8] In this regard, predicting the formation of acute pancreatic and peripancreatic fluid collections after AP will contribute the treatment and follow-up of AP.

METHODS

Ethical approval for the study was received from Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1104). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Population

Adult patients aged over 18 years old applyed to Ankara City Hospital and diagnosed with AP by emergency internal medicine clinic between January 2020 and November 2021 included in the study. The data of 438 patients were evaluated retrospectively through the hospital information processing system (HICAMP®). Patients with a history of chronic pancreatitis, malignancy, abdominal surgery and pregnancy were not included in the study. The relationship between acute fluid development after AP and hematological/biochemical parameters was investigated.

Definitions

The diagnosis of AP was confirmed for all patients by emergency internal medicine clinic doctor according to the Revised Atlanta Classification Criteria. For the AP diagnosis; at least two of the following criteria were required: presence of a typical abdominal pain, presence of more than 3-fold increase in serum amylase or lipase levels and characteristic radiological imaging findings.[7]

Complete blood count was performed with Sysmex XE-2100 (SysmexCorp.®Kobe, Japan) automated hematology analyzer, CRP test was performed with BN II analyzer (DadeBehring/Siemens®, Germany), other parameters were measured with a modular analyzer (Cobas 8000 Roche®, Mannheim, Germany).

Data Collection

Demographic information, AP etiologies, co-morbidities, medications, hematological and biochemical parameters at the time of admission to the hospital (WBC, Hb, RDW, NEU, LYM, PLT, total and direct bilirubin, albumin, uric acid, triglyceride, LDL cholesterol, calcium, ALP, GGT, AST, ALT, amylase, lipase, CRP, procalcitonin) were recorded from HICAMP®.

The contrast-enhanced abdominal computed tomography (CACT) imaging reports of the patients taken at the time of admission and within 48-72 hours of follow-up were checked from hospital imaging system for invastigating whether patients have acute pancreatic/peripancreatic fluid or not.

Statistical Analysis

To investigate whether biochemical and hematological measurements were statistically significant in distinguishing between the patients with and without fluid development, calculating the area under the ROC curve (AUC) and 95% confidence intervals (CI) was used. If the AUC were found to be significant, the points where the sum of the sensitivity and selectivity levels reached the maximum were accepted as the best (optimal) cut-off points. Then, sensitivity, selectivity, positive and negative predictive values, and diagnostic accuracy rates at optimal cut-off points were calculated.

The factors that may be most decisive in distinguishing between the patients with and without fluid development were determined by multivariate forward stepwise logistic regression analysis. All variables detected as $p<0.10$ as a result of univariate statistical analysis were included in the regression model as candidate risk factors. Variables that were not considered clinically important and those with multicollinearity problems were excluded from the model. Additionally, odds ratios, 95% CI and Wald statistics were calculated for each variable included in the final model.

For data analysis IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY, USA) package program was used. Results were considered statistically significant for $p<0.05$.

RESULTS

Of the 438 patients included in the study, 220 (50.2%) were male and 218 (49.8%) were female. The age of the patients ranged between 19 and 96 years (56.73±29.6). While AP was most commonly due to biliary causes (74.2%), the second most common reason was idiopathic causes (13%). When classified according to severity, 380 (84.9%) of the patients were evaluated as acute interstitial edematous pancreatitis (AIOP) and 58 (15.1%) as necrotizing pancreatitis (NP). It was observed that 8 (1.82%) of the patients included in the study died after follow-up due to AP.

It was determined that patients with fluid development after AP were younger and mostly in male gender ($p=0.045$; $p=0.003$, respectively). The rate of hypertriglyceridemic etiology was statistically significantly higher in the patients with fluid development ($p=0.014$). There was no statistically significant difference between the groups in terms of comorbidities and medication use ($p>0.05$).

Table 1. Biochemical and hematological values according to patients with and without fluid development

	Without fluid	With fluid	p-value
Total bilirubin (mg/dl)	0.98 (0.65-2.72)	1.19 (0.68-2.43)	0.918
Direct bilirubin (mg/dl)	0.53 (0.25-1.90)	0.60 (0.25-1.40)	0.869
Albumin (g/L)	41.00 (38.00-44.20)	41.62 (37.24-44.77)	0.961
Uric acid (mg/dl)	5.20 (4.20-6.23)	5.50 (4.50-7.00)	0.038
Triglyceride (mg/dl)	105.50 (83.25-154.75)	102.00 (79.00-144.75)	0.346
LDL cholesterol (mg/dl)	93.00 (71.00-120.00)	92.00 (71.00-113.00)	0.498
Calcium (mg/dl)	9.20 (8.80-9.50)	9.00 (8.55-9.40)	0.010
ALP (U/L)	126.00 (86.00-233.00)	111.00 (81.00-172.00)	0.007
GGT (U/L)	164.00 (59.00-423.25)	154.00 (49.00-408.50)	0.618
AST (U/L)	115.00 (37.00-239.00)	74.00 (28.00-212.00)	0.104
ALT (U/L)	132.00 (35.00-305.00)	93.00 (31.00-262.00)	0.212
Amylase (U/L)	697.00 (290.00-1468.00)	952.00 (311.00-1774.00)	0.168
Lipase (U/L)	983.00 (365.00-2078.00)	1149.00 (375.00-2552.00)	0.243
CRP (mg/dl)	16.50 (7.00-40.25)	63.50 (23.50-132.75)	<0.001
Procalcitonin (µg/L)	0.08 (0.03-0.20)	0.11 (0.04-0.42)	0.016
WBC ($\times10^9$/L)	9.85 (7.69-12.80)	12.19 (9.00-15.39)	<0.001†
Neutrophil ($\times10^9$/L)	7.59 (4.97-10.36)	9.80 (6.62-13.43)	<0.001†
Lymphocyte ($\times10^9$/L)	1.47 (1.00-1.93)	1.25 (0.83-1.77)	0.029†
Hemoglobin (g/dl)	13.36±1.70	13.84±2.02	0.008‡
Platelet ($\times10^9$/L)	253.00 (209.50-302.50)	250.00 (208.00-309.00)	0.966†
RDW (%)	14.00 (13.30-14.70)	14.00 (13.40-14.90)	0.546†

Descriptive statistics; They are shown as median (25th percentile-75th percentile) or mean ± standard deviation. † Mann Whitney U test, ‡ Student's t test.

Compared to laboratory measurements it was found that WBC, neutrophil, CRP and procalcitonin levels were statistically significantly higher (p<0.001; p=0.008; p=0.038 and p=0.016 respectively) and calcium, ALP levels were statistically significantly lower (p=0.010 and p=0.007) in patients with fluid development (Table 1).

Compared to other laboratory measurements it was also detected that CRP/Albumin, neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) levels were higher (p<0.001; p<0.001 and p=0.033) in patients with fluid development (Table 2).

Table 2. Other proportional values according to patients with and without fluid development

	Without fluid	With fluid	p value
Albumin/bilirubin	38.94 (12.87-63.08)	31.93 (13.01-57.75)	0.686
Albumin/platelet	0.16 (0.13-0.19)	0.16 (0.13-0.19)	0.622
RDW/platelet	0.06 (0.05-0.07)	0.06 (0.05-0.07)	0.945
CRP/albumin	0.46 (0.18-1.04)	1.70 (0.60-3.81)	<0.001
Neutrophil/ lymphocyte	4.98 (2.61-8.84)	7.55 (3.96-14.30)	<0.001
Platelet/ lymphocyte	178.34 (131.34-253.27)	205.45 (137.50-297.87)	0.033

Descriptive statistics; Shown as median (25th percentile-75th percentile). † Mann Whitney U test.

To distinguish the patients with and without fluid development the area under the ROC curve was found to be statistically significant for WBC, uric acid, calcium, ALP, CRP, procalcitonin, CRP/Albumin, NLR and PLR measurements respectively (Table 3). The ROC curve for WBC, CRP, and CRP/Albumin ratio is shown in Figure 1.

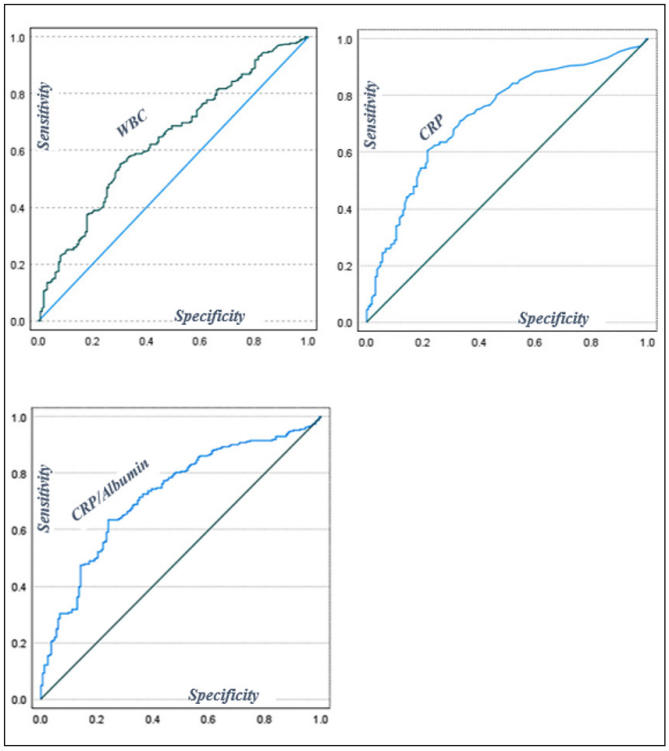

Figure 1. ROC curves for WBC, CRP, and CRP/Albumin respectively.

Table 3. ROC analysis results for laboratory values in distinguishing patients with and without fluid development

	AUC	95% CI	p-value
White blood cell	0.639	0.586-0.692	<0.001
Uric acid	0.559	0.504-0.614	0.034
Calcium	0.574	0.520-0.628	0.008
ALP	0.577	0.520-0.633	0.008
CRP	0.730	0.681-0.778	<0.001
Procalcitonin	0.568	0.514-0.623	0.014
Albumin/bilirubin	0.512	0.455-0.568	0.688
Albumin/platelet	0.514	0.458-0.570	0.621
RDW/platelet	0.502	0.446-0.558	0.945
CRP/albumin	0.724	0.676-0.773	<0.001
Neutrophil/lymphocyte	0.631	0.577-0.685	<0.001
Platelet/lymphocyte	0.561	0.506-0.616	0.029

AUC: Area under the curve, CI: Confidence Interval

The most predictive factors in distinguishing the patients with and without fluid development were examined with multivariate logistic regression analysis. According to the forward stepwise elimination method, the most determining factors in distinguishing groups with and without fluid development were CRP/Albumin ratio, ALP, age, WBC and PLR (Table 4).

Regardless of other factors, CRP/Albumin ratio greater than 1.04 increased the risk of fluid development 6.2 times (95% Cl: 3.808-10.366 and p<0.001) while ALP below 199.5 U/L incrased 2.5 times (95% Cl: 1.505-4.226 and p<0.001) and younger age incrased 0.9 times (95% Cl: 0.965-0.991 and p<0.001) (Table 5).

Table 5. The most predictive factors in differentiating patients with and without fluid development

	Odds ratio	95% CI	Wald	p value
CRP/albumin >1.0482	6.282	3.808-10.366	51.737	<0.001
ALP <199.5 U/L	2.522	1.505-4.226	12.332	<0.001
WBC >11.685×10^9/L	1.938	1.210-3.103	7.592	0.006
Age	0.978	0.965-0.991	11.507	<0.001
Platelet/lymphocyte >197.146	1.596	1.012-2.519	4.044	0.044

CI: Confidence Interval

Evaluating separately the patients with APFC and ANC, it was found that while the most determining factors in distinguishing the patients with APFC were CRP/Albumin ratio, ALP, age and WBC, they were CRP/Albumin ratio, WBC, ALP, calcium and age in patients with ANC.

Regardless of other factors, CRP/Albumin ratio greater than 1.04 significantly increased the risk of ANC 10.9 times (95% Cl: 4.813-24.770 and p<0.001) when ALP below 199.5 U/L increased 4.4 times (95% Cl: 1.676-12.031 and p=0.003). Also there was a statistically significant inverse association between age and ANC development (Odds ratio=0.974; 95% CI: 0.955-0.993 and p=0.008). On the other hand, it is found that calcium level below 8.6 mg/dl increased developing ANC 3 times (95% CI: 1.424-6.331 and p = 0.004).

DISCUSSION

Acute pancreatitis is still an important disease that causes serious morbidity and mortality all over the world.[2,3] When the incidence of AP is between 13-45/100,000, its mortality is reported to be approximately 1%. However, in cases of severe pancratitis with organ failure and infection, mortality may vary between 20-40%.[8,9]

In several studies, it was observed that 70-80% of AP cases were AIOP and approximately 20-30% were ANP.[3,4] In our study it was found that 84.9% of the patients were AIOP and 15.1% were ANP. Our results were close to the rates obtained from the literature.

In the literature, the incidence of fluid development after AP was observed as 30-50% and it was found that 50% of cases with fluid development regressed spontaneously within the first week, while 30-50% turned into pseudocyst.[10] While the rate of ANC development after AP was observed as 20-40% and the rate of WON development as 1-9%, Manrai et al.[11] showed that 57.8% of AP cases developed ANC and progressed to WON.[12,13]

Table 4. The best cut-off points of ROC analysis in distinguishing patients with and without fluid development and the diagnostic performance indicators at these points

	Best cut	Sensitivity	Selectivity	PTD	NTD	Accuracy
White blood cell	>11.685×10^9/L	152/275 (55.3%)	113/162 (69.8%)	152/201 (75.6%)	113/236 (47.9%)	265/437 (60.7%)
Uric acid	>6.45 mg/dl	95/275 (34.5%)	131/162 (80.9%)	95/126 (75.4%)	131/311 (42.1%)	226/437 (51.7%)
Calcium	<8.695 mg/dl	86/275 (31.3%)	136/163 (83.4%)	86/113 (76.1%)	136/325 (41.8%)	222/438 (50.7%)
ALP	<199.5 U/L	225/275 (81.8)	53/163 (32.5%)	225/335 (67.2%)	53/103 (51.5%)	278/438 (63.5%)
CRP	>44.5 mg/dl	166/274 (60.6%)	127/35 (78.4%)	166/201 (82.6%)	127/235 (54.0%)	293/436 (67.2%)
procalcitonin	>0.255 µg/L	96/274 (35.0%)	131/162 (80.9%)	96/127 (75.6%)	131/309 (42.4%)	227/436 (52.0%)
CRP/Albumin	>1.0482	174/274 (63.5%)	123/162 (75.9%)	174/213 (81.7%)	123/223 (55.2%)	297/436 (68.1%)
Neutrophil/lymphocyte	>6.428	159/275 (57.8%)	102/162 (63.0%)	159/219 (72.6%)	102/218 (46.8%)	261/437 (59.7%)
Platelet/lymphocyte	>197.146	145/275 (52.7%)	100/162 (61.7%)	145/207 (70.0%)	100/230 (43.5%)	245/437 (56.1%)

GP: True Positive, FN: False Negative, GN: True Negative, FC: False Positive, N: Total number of cases, PTD: Positive predictive value, NTD: Negative estimated value.

Compared to the literature data, in our study WON development was higher and pseudocyst development was lower. It was thought it is due to the difference in the interpretation of imaging examinations and in the demographic and clinical characteristics of the patients.

There are few studies in the literature on predictive factors for fluid developments after AP. Most of these studies include old terminologies used before Revised Atlanta Classification such as pancreatic abscess and also the hematologic/biochemical parameters examined were limited.[5,6,14]

In a study conducted by Cui et al.[1] in China with 302 patients, younger age and alcoholic etiology were found to be statistically significant for development of pancreatic fluid collection. In a another study conducted by Diculescu et al.[5] in Romania with 62 patients was observed that presence of ascites in the patient was associated with acute fluid collection and alcoholic etiology and low serum ALP level were associated with pseudocyst formation.

Also in a study conducted by Poornachandra et al.6 in India with 65 patients observed that male gender, presence of ascites at at the time of admission, presence of palpable mass in the abdomen and high CTSI were significant predictive values for pseudocyst formation. Additionally, Manrai et al.[11] stated a relationship between high BUN, serum creatinine ratio, BISAP, APACHE score and presence of organ failure in fluid development after AP, but did not find a statistically significant evidence in terms of age and gender.

In our study it was found that fluid development was statistically significantly higher in male gender and younger patients. Our results are similar with the data obtained by Cui et al.[1] and Poornachandra et al.[6] regarding fluid and pseudocyst formation after AP.

When our study was evaluated according to the etiology of AP, it was found that patients with AP due to hyperthyroglyceridemia had more fluid development compared to other etiologic reasons. Our results were consistent with literature data showing AP cases due to hypertriglyceridemia are more severe.[15,16] Accordingly, our study differs from the studies of Cui et al.[1] and Diculescu et al.[5] found a relationship between fluid and pseudocyst development after AP with alcoholic etiology. It was thought that the reason of the difference was due to alcohol was the most common etiologic cause of AP in both studies while it was in limited number of cases in our study (4.1%).

Hypercalcemia plays a role in the etiology of AP by disrupting intracellular defense mechanisms with increased cytosolic calcium level in pancreatic acinar cells and causing early trypsinogen activation.[17] However, hypocalcemia develops in patients with AP. The development of hypocalcemia in AP is attributed to calcium salts, hypomagnesemia and transient hypoparathyroidism caused by free fatty acids released after digestion of mesenteric adipose tissue by pancreatic enzymes in the early phase, while it is attributed to inflammatory response and sepsis in the late phase. It has shown that low serum calcium level indicates severe inflammatory response and organ failure and is a predictive parameter for severe AP.[14] So that, serum calcium level is also used in Ranson and Glasgow-Imrie scoring.[18]

Studies investigating the relationship between serum calcium level and fluid development after AP are very limited in the literature. In a study conducted in by Akgül et al.[14] scanned total of 102 patients diagnosed with AP and found that low serum calcium level (<8 mg/dl) was a significant predictive factor in pseudocyst development.

In our study, serum calcium level was statistically significantly lower in the patients with fluid development but the predictive value was found to be low (p>0.001). However it was found that calcium level below 8.6 mg/dl increased the risk of developing ANC by 3-fold. This result supports that low serum calcium level can be used as an important predictive factor to indicate the development of ANC after AP.

Alkaline phosphatases are a group of glycoproteins in the liver, kidney, intestines, bone, placenta, pancreas and WBC and there are many studies in the literature indicating that high serum ALP levels can be used as a predictive factor in the diagnosis and severity of AP.[19] However, recent studies have also shown that serum intestinal ALP level decreases in inflammatory and septic conditions and may be used in the treatment of some inflammatory diseases.[20]

Diculescu et al.[5] observed that serum ALP level was lower in patients with pseudocyst formation after AP. They stated that serum ALP level below 185 U/L could be used as a predictive factor with 90% specificity in pseudocyst formation after AP, but they did not report any opinion to explain about the relationship between low serum ALP level and developing pseudocyst.

In our study, serum ALP level was statistically significantly lower in patients with fluid development after AP. It was found that ALP levels below 199.5 U/L significantly increased fluid developpent by 2.5 times after AP. However it was seen that, excluding the group developed APFC, ALP levels below 199.5 U/L significantly increased developing ANC by 4.5 times.

According to our results, low serum ALP level can be used as a predictive factor especially in ANC formation. However, we think that the relationship between developing fluid/pseudocyst after AP and low ALP level should be supported by more comprehensive studies and the reasons should be discussed.

There are many studies about hematologic parameters as acute inflammation parameters in the literature.[21] In recent years NLR has been studied extensively in various diseases as a new inflammation parameter. It was also shown that NLR has a high predictive value in predicting the severity of AP, but there is no study on the prediction of fluid development after AP.[22]

Kaplan et al.[23] investigated the relationship between the prognosis and mortality of AP with NLR-PLR combination and they found that NLR-PLR combination had superior predictivity in terms of prediction of mortality compared to Ranson, Atlanta, and Bisaps scoring system. In another study, Dancu et al.[24] showed that NLR examined at 48 hours had a high predictive value in predicting the severity of AP but was not superior to BISAP.

In our study, NLR was found to be higher in patients with fluid development and was statistically significant in differentiating the patients. Considering NLR is an indicator of inflammation, it was related to the patients with fluid development were classified into moderate and severe AP according to the Revised Atlanta Classification.

There are several studies showed that PLR can be used as an effective predictive factor in demonstrating severity in AP.[25,26] But there is no study in the literature investigating the relationship between PLR and fluid development after AP.

We found that PLR above 197.146 increased fluid development by 1.5 times but it had a lower sensitivity than NLR and CRP/albumin values. However it is important to state that, PLR can be used as a predictive value in the fluid development after AP.

PCT is an acute phase reactant increases in bacterial infections and non-bacterial systemic inflammatory responses. Also it can be used in predicting severity in AP, organ failure after AP and infected necrosis.[27] There is no study in the literature investigating the relationship between serum PCT levels and fluid development after AP. In our study, PCT levels were found to be higher in patients with fluid development and can be used in differentiating the patients with fluid development.

CRP is one of the most widely used acute phase reactants to demonstrate infective and non-infective inflammation with the advantages of being easy to study and inexpensive all over the world.[28] In addition to its use as a parameter in the Ranson criteria, there are many studies in the literature regarding the prediction of severity of AP by CRP. According to these studies, it has been shown that CRP levels at 48 hours after admission, has a high predictive value in the determination of severity in AP.[29]

In a prospective study, Vinish et al.[30] found that serum CRP level >150 mg/dl can be used as a predictive factor in the development of pancreatic fluid. Also Cui et al.[1] stated that the presence of high serum CRP level at 48 hours along with young age and alcoholic etiology to be significant as a predictive factor for the development of pancreatic fluid collection after AP.

In our study, CRP level was found to be significant in differentiating patients with and without fluid development after AP, but its sensitivity and specificity were low.

CRP/albumin ratio can be used as an inflammatory marker in various diseases and AP.[31,32] In a retrospective study it was shown that the mortality risk was 19.3 times higher in patients with a CRP/albumin ratio ≥16.28 and in another study CRP/albumin ratio was found to be 90% sensitive (cut-off value of 8.51) in determining the severity of AP.[33,34]

In our study, it was found that CRP/albumin ratio greater than 1.04 increased the risk of fluid development by 6.2-fold and increased the risk of ANC itself by 10.9-fold. According to our results, CRP/albumin ratio can be used in predicting fluid development after AP with high predictive value.

There are several limitations in this study. Although it has a higher sample size compared to similar limited studies in the literature, it is a retrospective, single-center study. So that a selection bias may be existed, even though the clinical data were derived from a prospectively maintained database. Hence, randomized, multicenter prospective studies are needed.

CONCLUSION

It has been determined that male gender and younger age may be a risk factor for development of acute fluid collections after AP. Also presence of high CRP/albumin ratio, high NLR and low serum ALP level can be used as an indicator in predicting of acute pancreatic and peripancreatic fluid development. Additionally, the presence of hypocalcemia has a high predictive value in predicting the development of ANC itself.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 22.12.2021, Decision No: E2-21-1104).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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